Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter. Specific support for the recitation of the ability to enhance vascular permeability is at least found in Example 85.

Prior to the present amendment, claims 39-44 were pending in this application and were rejected on various grounds. Claims 44 has been cancelled without prejudice. The rejection to the remaining claims is respectfully traversed.

IDS

Applicants resubmit a copy of the PTO Form 1449 filed on 4/11/02 and a supplemental IDS for all documents, which is in compliance with 37 C.F.R. 1.98(a)(1), listing the authors, title and publication date to overcome this rejection.

Claim Rejections - 35 USC § 101

Claims 39-44 were rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility." The rejection is respectfully traversed.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the results of the vascular leak assay described in the present application are sufficient to establish a specific, substantial and credible utility for the PRO302 polypeptide. These data were first disclosed in international application PCT/US98/19177 filed September 14, 1998, to which priority is claimed in this application.

Example 85 (page 215, lines 29) describes a dye-based vascular permeability assay in which PRO302 has been demonstrated to induce vascular leakage or permeability in guinea pig

skin vasculature using the Evans blue dye (Miles assay). Here, the test molecule PRO302, is injected intradermally into the skin on the back of the animals whereas the Evans blue dye is injected intracardially into the guinea pigs. Skin vascular permeability response to PRO302 is visually scored by measuring the diameter of the blue-colored leaks 1 to 6 hours after the test polypeptide is administered. Dye-based vascular permeability assays utilizing dyes like Evans blue are routinely used in the art to estimate vascular leakage to correlate this actvity with disease or to evaluate the vascular permeabilizing function of a given substance (see exhibits Wei et al., Wise et al., and Collins et al; all enclosed with IDS). For example, in Collins et al., VPF (vascular permeability factor) was identified using a plasma leakage assay in rabbit skin and the findings were correlated with angiogenesis and microcvascular permeability changes *in vivo*.

During vascular permeability, there is an increase in permeability of capillary vessels to different macromolecules, like plasma proteins, including fibrinogen and other clotting factors to generate stroma. As a result, the extravasated plasma fibrinogen rapidly clots to form an extravascular gel of crosslinked fibrin which dramatically alters the local microenvironment, transforming the so far inert extravascular matrix of normal adult tissues into a proangiogenic provisional matrix that favors and apparently stimulates inward migration of host mesenchymal cells and vascularization. Such events occur for example, during wound healing as well as in pathologic conditions like tumor formation, etc. For example, the enclosed reference Collins et al. indicated that VPF or vascular permeability factor could be useful as a homeostatic regulator of microvascular permeability under physiological conditions and additionally, as a component of an inflammatory response, forming part of the host defense function of cells (see Collins, last paragraph bridging page 198, column 2 and page 199, column 1). Subsequent knowledge in the art on VPF, now generally referred to as Vascular Endothelial Growth Factor (VEGF) has burgeoned. VEGF has been shown to play many important biological roles and is involved in various diseases, including tumor angiogenesis, endothelial cell growth, age-related macular degeneration (AMD), etc. Similarly, a variety of real-life utilities are envisioned for PRO302 based on the vascular permeability assay results.

Accordingly, agents capable of inducing vascular permeability like PRO302 can be used, for example, to therapeutically induce wound healing in a given target tissue and are therefore, promising drug candidates. Alternatively, antibodies raised against PRO302 can be useful in diagnosing target tissue disorders. Thus, Applicants have asserted a specific substantial utility for PRO302 that is well supported in the specification.

In assessing the value of the vascular permeability data in the specification, the Examiner notes that: "it does not give the actual data or indicate the relative activity of the PRO302 protein compared to the positive control.....the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability. It is further noted that the observed activity is not unique to PRO302 in that at least one other protein and the positive control both induced vascular permeability in the guinea pig model. Because no specific and substantial or well-established utility has been demonstrated for the protein.....one of skill in the art would not be able to recognize a specific and established utility for the claimed antibodies."

In the specification, at page 216, line 3, the relative activity of the PRO302 protein has been compared to a positive control; the specification discloses that "(b)lemishes of at least 5 mm in diameter are considered positive for the assay when testing purified proteins, ... A response greater than 7 mm diameter is considered positive for conditioned media samples. Human VEGF at 0.1 μg/100 μl is used as a positive control, inducing a response of 15-23 mm diameter." Applicants additionally disclose on page 216, line 7 that PRO302 tested positive for the vascular leak assay.

Whether or not the observed activity of PRO302, as a vascular permeability inducer, is 'unique' is completely irrelevant for assessing patentable utility. As it should be apparent from the earlier discussion of legal standard, the requirement that the utility must be specific does not mean that no other compound can have the same utility (biological property). Following the Examiner's rationale, no new anti-cancer, anti-inflammatory, etc. molecules would be patentable since there are known compounds with similar properties. Obviously, this outcome is not intended, and this conclusion should not be reached if the legal standard is applied properly.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. Indeed, the Applicants' assertion that PRO302 is an inducer of vascular permeability based on the guinea pig vascular permeability assay is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art. Based on the teachings in the specification, and the general knowledge that agents inducing vascular permeability may be useful candidates for modulating wound healing, one of skill in the art would clearly recognize regulatory uses for the PRO 302 polypeptide in wound healing and its antibodies as a diagnostic tool to identify diseases associated with tumor formation. Of course, it is always possible that an invention might fail on its way of development to a commercial product. For example, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections- 35 U.S.C.§112, second paragraph

Claim 44 was rejected under 35 U.S.C. §112, second paragraph, allegedly for being vague and indefinite in defining the term "specifically binds to."

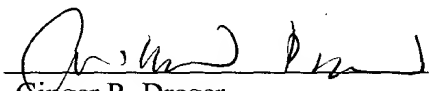
Without acquiescing to any rejection, claim 44 has been cancelled and hence, this rejection is moot for this claim. Claim 39 has been amended to recite "specifically bind to." Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Accordingly, the present rejection is believed to be moot, and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C40). Please direct any calls in connection with this application to the undersigned at the umber provided below.

Respectfully submitted,

Date: May 27, 2003



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